



12 February 1999

Dr. Kenneth Olden, Director
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Dear Dr. Olden:

We the undersigned are writing to commend you for requesting last year that the National Toxicology Program (NTP) Board of Scientific Counselors *Report on Carcinogens* Subcommittee undertake a second review of the proposed listing of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) in the 9th *Report on Carcinogens* during its December 2, 1998 meeting. We also wish to commend the members of the Subcommittee for their substantial efforts to ensure that their re-review of the proposed TCDD listing was thoughtful, comprehensive, and solidly grounded in the voluminous body of scientific information regarding TCDD toxicity that has been painstakingly gathered over the past twenty years. We congratulate the Subcommittee on the wisdom of its decision to recommend continued listing of TCDD as *reasonably anticipated to be a human carcinogen* in the 9th *Report on Carcinogens*.

It is appropriate to briefly summarize the principal reasons why TCDD cannot at present be credibly listed as *known to be a human carcinogen*. First, in February 1997 an International Agency for Research on Cancer (IARC) Working Group concluded that it was not possible to establish a causal relationship between TCDD exposure and increased cancer mortality based on the available human data because of 1) the weakness of the reported associations; 2) the fact that little epidemiologic precedent exists for a causal risk factor that would elevate all cancer mortality without also producing even stronger associations with mortality from particular cancer types; and 3) the inability to exclude confounding by other potentially important exposures such as asbestos, tobacco smoke, and 4-amino-biphenyl, from some of the reported associations. The IARC Working Group report appropriately concluded that "there is *limited evidence* in humans for the carcinogenicity of TCDD."

Second, while additional epidemiologic studies of TCDD exposure have appeared in the peer-reviewed literature since the IARC review was completed, the key data from virtually all of these reports were published in preliminary form prior to the IARC review and were cited in the IARC Working Group's report as well as in the NTP Background Document for TCDD. The small amount of truly new epidemiologic information that has appeared since the IARC review was discussed during the *Report on Carcinogens* Subcommittee meeting on December 2, 1998, and the Subcommittee concluded that this new information does not support any change in the classification of TCDD with respect to human carcinogenicity. At the present time, the epidemiologic evidence regarding TCDD continues to be *limited*.

Third, the mechanistic evidence regarding TCDD's carcinogenic potential is insufficient to

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overcome the significant uncertainties of the epidemiologic evidence. The mechanism(s) by which TCDD causes cancer in laboratory animals or might cause cancer in humans is still largely unknown. While receptor binding may be necessary for many of TCDD's effects, there is a poor correlation between Ah receptor occupancy and the full spectrum of toxicities that have been observed in laboratory animals following TCDD exposure. At the present time, it is not possible to predict what, if any, toxic response might occur in a specific tissue in any given species solely on the basis of Ah receptor presence, functionality, and occupancy by TCDD. As some of us stated previously when we urged the *Report on Carcinogens* Subcommittee not to upgrade the classification of TCDD during its first review of this topic in October 1997:

"Ah receptor occupancy by TCDD is just one, albeit very important, early step in a multiple pathway web of interaction that may or may not, in any given situation, lead to a toxic response. Lack of understanding of the complex molecular events downstream from receptor occupancy that might or might not culminate in malignancy prevents one from concluding on mechanistic grounds that TCDD is a *Known Human Carcinogen* at the present time."

28 October 1997 letter from Sutter *et al.* to NTP *Report on Carcinogens* Subcommittee

Again, we wish to congratulate you for your efforts to ensure an objective and comprehensive evaluation of the scientific evidence regarding TCDD. We completely support the well-reasoned conclusion that this substance should continue to be classified as *reasonably anticipated to be a human carcinogen*.

Sincerely,

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